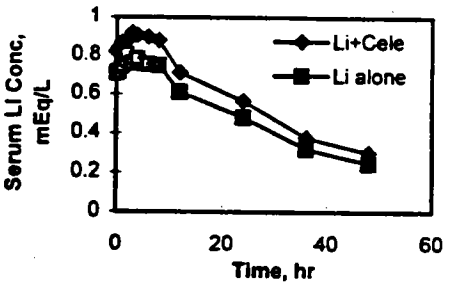
Reviewer's comment:
This is a short term study with respect to celecoxib. Since long term use of celecoxib may affect the renal function there is a potential for reduced clearance of methotrexate after chronic use of celecoxib.

Lithium (Study 038)

Lithium is eliminated via renal excretion. NSAIDs such as indomethacin and piroxicam have been reported to increase steady-state plasma concentrations of lithium. Lithium levels of 1.5-2.5 mEq/L have been associated with mild to moderate adverse reactions (diarrhea, vomiting, drowsiness, muscular weakness and lack of coordination). It is considered a safe measure to maintain lithium level in patients below 1.5 mEq/L (~10.4 μg/mL).

This study assessed the effect of coadministration of celecoxib 200 mg BID on the steady-state pharmacokinetics of lithium, administered as controlled-release Eskaith® 450 mg BID. The study also assessed the effect of coadministration of controlled release Eskaith on the steady-state pharmacokinetics of celecoxib. Twenty-four healthy subjects completed the study. Subject received three treatments in a crossover fashion: Eskaith® CR 450 mg BID plus celecoxib 200 mg BID, Eskaith® CR 450 mg BID alone and celecoxib 200 mg BID alone. The detailed study design is given in Appendix 1 (p. 132).

Effect of celecoxib on lithium pharmacokinetics: Mean serum lithium levels were higher when lithium was coadministered with celecoxib. The highest serum level for any subject was 1.436 mEq/L (3 hours after the last dose of lithium+celecoxib in Subject #20). There were statistically significant differences between treatments for mean AUC_{0-12}, AUC_{0-48}, and Cmax with values being higher for subjects receiving lithium+celecoxib than lithium alone. Mean renal clearance was 13% lower when lithium was coadministered with celecoxib. Ratios of mean pharmacokinetic parameters and their 90% confidence intervals are tabulated below.

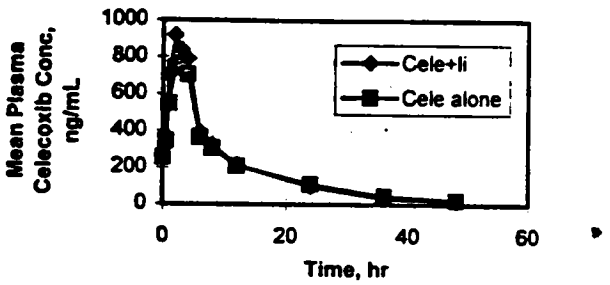


Lithium Mean Parameter Values (± SD)

Parameter	Lithium+Celecoxib	Lithium alone	Ratio[1] (%)	90% CI
AUC_{0-12} (mEq.hr/L)	10.28 ± 2.08	8.82 ± 1.92	116.7*	111.9 - 121.7
AUC_{0-48} (mEq.hr/L)	27.61 ± 6.72	23.58 ± 6.11	117.6*	113.3 - 122.0
Cmax (mEq/L)	0.99 ± 0.19	0.85 ± 0.18	115.9*	108.6 - 123.6
Tmax (hr)	4.47 ± 2.40	3.63 ± 2.65	123.1	-
CL_{renal} (L/hr)	1.16 ± 0.25	1.33 ± 0.32	87.3*	81.3-93.9
Urinary Excretion Rate, 0-24 hr (mg/hr)	5.43 ± 0.86	5.10 ± 0.82	106.6	-

[1]Ratio: (Lithium+celecoxib) vs. lithium alone; *Significant difference ($p<0.05$)

Effect of lithium on celecoxib pharmacokinetics: Mean plasma celecoxib concentrations were higher for the first 6 hours postdose when celecoxib was coadministered with lithium than when it was administered alone. Plasma concentrations were comparable thereafter between the two treatments. The mean pharmacokinetic parameter values for the two treatments, their ratios and the corresponding 90% confidence intervals are tabulated below. There are no statistically significant differences between the two treatments ($p>0.05$).



Celecoxib Mean Parameter Values (±SD)

Parameter	Celecoxib + Lithium	Celecoxib alone	Ratio	90% CI
AUC_{0-48} (ng.hr/mL)	8932± 4113	8696 ± 3611	102.2	96.4 - 109.5
Cmax (ng/mL)	996.1 ± 385.8	850.7 ± 296.0	115.2	101.5 - 130.9
Tmax (hr)	2.4 ± 0.8	2.8 ± 1.0	85.8	-

Conclusion:

- Coadministration of lithium with celecoxib 200 mg BID increased (17%) mean serum lithium concentrations which is similar to other NSAIDs.
- Celecoxib AUC was not significantly altered by coadministration of lithium carbonate.

Tolbutamide (Study 051)

Tolbutamide, a sulfonylurea antidiabetic agent, is metabolized by CYP2C9. This study examined the single-dose pharmacokinetics of tolbutamide in the presence of celecoxib.

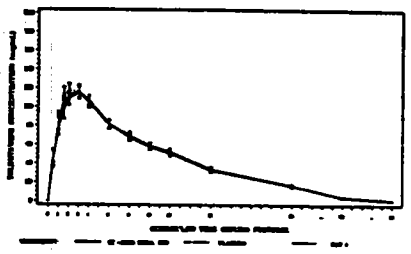
Sixteen healthy subjects participated in the study. On Day 0, after an overnight fast, subjects received a single oral dose of tolbutamide 1000 mg. Subjects were randomized to receive either celecoxib 200 mg BID or placebo BID on Days 2-7, then crossed over to the alternate treatment on Days 10-15. On Days 8 and 16, after an overnight fast, subjects received tolbutamide 1000 mg with the morning dose of celecoxib or placebo. The detailed study design is given in Appendix 1 (p. 140).

Celecoxib plasma concentrations: In this study, the mean $AUC_{0-12\,hr}$, C_{max}, and T_{max} values for celecoxib were in agreement with those reported in previous studies (AUC_{0-12hr}: 8232.9±3324.6 ng/mL*hr; Cmax: 1269.8±516.9 ng/mL; Tmax: 3.1±1.5 hrs).

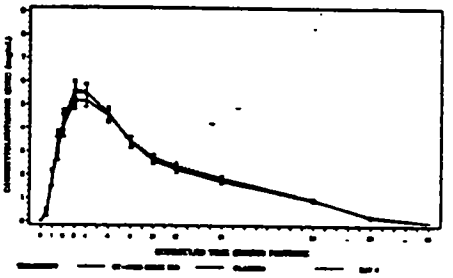
Tolbutamide: When tolbutamide was administered alone, mean plasma concentrations peaked at approximately 2 hours postdose for tolbutamide (117.3 μg/mL), 4 hours postdose for both carboxytolbutamide (5.65 μg/mL) and hydroxytolbutamide (1.76

μg/mL). At 48 hours postdose, the plasma concentrations for tolbutamide and its metabolites were very low (1.51 μg/mL for tolbutamide and below the quantitation limit for the metabolites). As shown in the figure below, similar profiles were observed when tolbutamide was administered with celecoxib 200 mg BID or placebo BID.

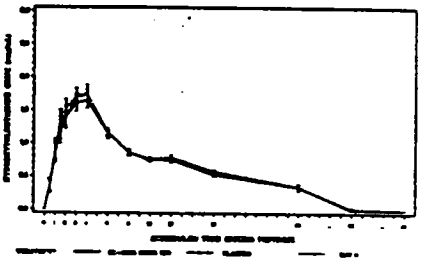
Tolbutamide



Carboxytolbutamide



Hydroxytolbutamide



The mean pharmacokinetic parameter values for all treatments are tabulated below.

Mean Parameter Values (±SD)

Parameter	Tolbutamide alone	Tolbutamide + Placebo BID	Tolbutamide + Celecoxib BID
Tolbutamide			
$AUC_{0-48\ hr}$ (μg/mL*hr)	1504.87 ± 339.4	1493.38 ± 342.31	1464.93 ± 324.96
C_{max} (μg/mL)	129.88 ± 22.10	131.00 ± 25.5	127.58 ± 19.40
T_{max} (hr)	2.3 ± 1.3	2.3 ± 1.1	2.4 ± 1.3
$XU_{0-48\ hr}$ (μg)	1059.9± 383.7	1004.9 ± 303.0	1113.7 ± 389.7
Carboxytolbutamide			
$AUC_{0-48\ hr}$ (μg/mL*hr)	72.13 ± 11.55	70.94 ± 14.42	68.97 ± 13.02
C_{max} (μg/mL)	5.99 ± 1.40	5.95 ± 1.48	5.74 ± 1.55
T_{max} (hr)	3.7 ± 1.1	3.5 ± 0.90	3.7 ± 1.1
$XU_{0-48\ hr}$ (μg)	632566 ± 141033	642153 ± 118408	636474 ± 110193
Hydroxytolbutamide			
$AUC_{0-48\ hr}$ (μg/mL*hr)	21.78 ± 2.98	21.71 ± 3.67	20.66 ± 4.24
C_{max} (μg/mL)	1.85 ± 0.45	1.84 ± 0.42	1.74 ± 0.52
T_{max} (hr)	3.6 ± 1.5	3.1 ± 1.0	3.6 ± 0.73
$XU_{0-48\ hr}$* (μg)	126560 ± 31879	124798 ± 26073	127238.0 ±

*Amount excreted in the urine from 0-48 hrs.

Following administration of celecoxib 200mg BID, the mean pharmacokinetic parameters of tolbutamide and its major metabolites, carboxytolbutamide and hydroxytolbutamide, were generally within 10% of values observed in the presence of placebo. Analysis of variance indicated no statistically significant treatment effects for Cmax, $AUC_{0-48\ hr}$ and $XU_{0-48\ hr}$. (See table below for ratios of treatment means and the corresponding 95% confidence intervals.)

Ratio* of Least Square Means and the Corresponding 95% CI

Parameter	Tolbutamide	Carboxytolbutamide	Hydroxytolbutamide
$AUC_{0-48\ hr}$ (μg/mL*hr)	98.42	97.46	94.46

C_{max} (μg/mL)	97.97	96.22	92.77
$XU_{0-48\ hr}$ (μg)	110.57	99.65	102.51

*Ratio based on (tolbutamide+celecoxib) vs. (tolbutamide+placebo)

Conclusion:
Administration of celecoxib 200 mg BID with tolbutamide did not significantly alter the single-dose pharmacokinetic profiles of tolbutamide and its major metabolites, carboxytolbutamide and hydroxytolbutamide, as compared to those observed in the presence of placebo.

Comments: This study was conducted in healthy subjects and, therefore, no pharmacodynamic measurements were taken.

Warfarin (Study 040)

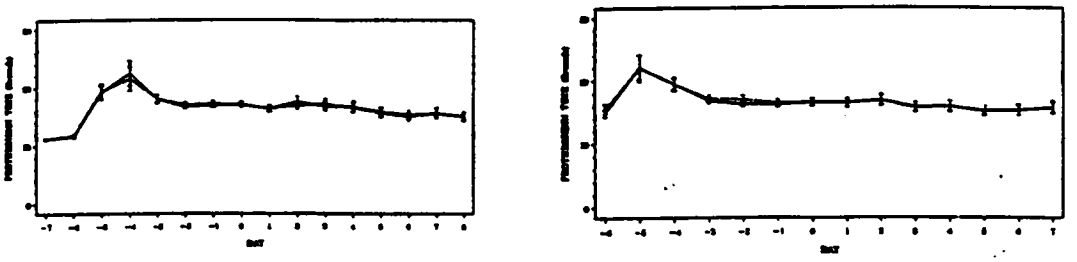
Warfarin, an anticoagulant, is highly protein bound and is primarily metabolized by CYP 2C9. The primary objective of this study was to assess the effect of multiple doses of celecoxib on prothrombin time (PT) and warfarin pharmacokinetics in subjects stabilized on warfarin.

Twenty-four healthy subjects participated the study. Warfarin dose was titrated for each individual to a target range of prothrombin time (Days -7 to -3). The individual dose was stabilized and ranged from 2 to 5 mg QD (Days -2 to 0). Subjects were then randomly assigned to one of the two groups to receive either celecoxib 200 mg BID or placebo BID concomitantly with warfarin (Days 1-7). The detailed study design is given in Appendix 1 (p. 146).

Mean trough celecoxib concentrations ranged from There was no significant day effect on celecoxib trough levels from Days 6-8, indicating steady state had been reached by Day 7.

Prothrombin time: As shown in the figures below, the mean prothrombin times as measured pre-dose and 11 hours postdose were similar between the two treatment groups (warfarin + celecoxib and warfarin + placebo). During the randomization period (Days 1-8), mean prothrombin times in both treatment groups gradually decreased (see figures and table below). Taking the values on Day 1 as the baseline, the changes in prothrombin time on various days (Days 2-8) were calculated for each individual. A repeated measures analysis did not detect a significant difference in the mean prothrombin time change between the two treatments ($p>0.3$).

Figure: Mean Prothrombin Times on Various Days (a) pre-dose, and (b) 11 hours post-dose
— warfarin + celecoxib; —— warfarin + placebo



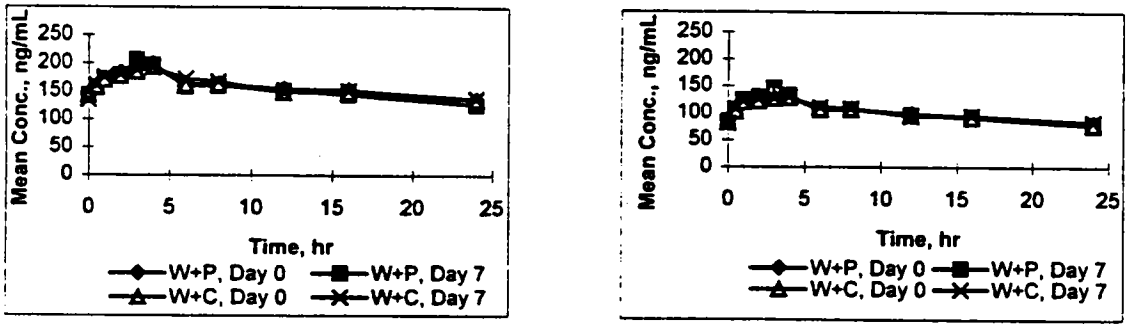
(a) Pre-Dose (b) 11 hrs Postdose

Table: Mean Prothrombin Times on Days 0, 1, 7 & 8

Treatment Day	Warfarin + Placebo		Warfarin + Celecoxib	
	Pre-dose	11 hrs Postdose	Pre-dose	11 hrs Postdose
0	16.95 ± 1.54	16.62 ± 1.97	17.97 ± 2.59	16.58 ± 2.21
1	16.31 ± 1.69	16.38 ± 2.23	16.28 ± 2.16	16.53 ± 2.36
7	15.59 ± 2.92	15.79 ± 3.21	15.52 ± 2.88	15.63 ± 3.04
8	14.94 ± 2.61	-	15.03 ± 2.36	-

***Warfarin pharmacokinetics*:** Stereospecific assay was performed to determine the plasma concentrations of both R- and S-warfarin. For easy assessment, the concentrations were normalized to a warfarin dose of 1 mg. As expected, the concentrations of the R-enantiomer were greater than those of the S-enantiomer.

(a) R-Warfarin (b) S-Warfarin



The dose-normalized mean pharmacokinetic parameter values (±SD) of R- and S-warfarin for Days 0 and 7 are tabulated below. Ratios of the least square means (warfarin + celecoxib vs. warfarin + placebo) and the corresponding 95% confidence intervals for both AUC and Cmax are also presented. Warfarin pharmacokinetics were comparable between the two treatment groups prior to the coadministration phase as evidenced by the Day 0 results ($p>0.8$). The Day 7 results indicated that there were no statistically significant differences between the two treatments ($p>0.2$).

Table: Mean Parameter Values (±SD) for Warfarin

Parameter	R-Warfarin		S-Warfarin	
	(Warfarin + Placebo) group	(Warfarin + Celecoxib) Group	(Warfarin + Placebo) group	(Warfarin + Celecoxib) Group
Day 0				
AUC_{0-24} (ng.hr/mL)	3818.7 ± 1403.6	3737.9 ± 810.55	2441.0 ± 986.5	2338.7 ± 744.2
Cmax (ng/mL)	205.8 ± 79.7	196.9 ± 38.7	139.8 ± 53.9	135.0 ± 34.3
Tmax (hr)	3.4 ± 0.8	4.3 ± 3.9	2.4 ± 1.2	2.6 ± 1.4
Day 7				
AUC_{0-24} (ng.hr/mL)	3588.0 ± 914.2	3853.4 ± 710.4	2475.2 ± 685.7	2485.0 ± 846.9
Cmax (ng/mL)	215.1 ± 95.7	207.9 ± 38.2	152.0 ± 77.0	137.9 ± 30.44
Tmax (hr)	3.5 ± 0.7	3.6 ± 1.5	2.6 ± 1.1	3.2 ± 1.6

Table: Ratio of least square means and 95% confidence intervals

Parameter	Day 0	Day 7
R-Warfarin		
AUC_{0-24} (ng.hr/mL)	101.7 (79.2, 103.9)	107.7 (94.6, 122.1)
Cmax (ng/mL)	100.6 (78.1, 129.8)	101.6 (89.1, 116.6)
S-Warfarin		
AUC_{0-24} (ng.hr/mL)	97.1 (72.6, 128.7)	101.7 (92.4, 112.2)
Cmax (ng/mL)	99.1 (77.0, 127.6)	99.0 (85.8, 114.4)

Conclusion:
Coadministration of celecoxib 200 mg BID did not significantly alter the steady-state pharmacokinetics of warfarin nor did it have significant effect on the prothrombin time in subjects taking warfarin 2 to 5 mg QD.

Glyburide (Study 039)

Glyburide, a second generation oral sulfonylurea hypoglycemic drug, is highly protein bound and has a small volume of distribution. The objective of this study was to determine the effect of multiple doses of celecoxib 200 mg BID on the steady-state pharmacokinetic and pharmacodynamic profile of glyburide in subjects with type II non-insulin dependent diabetes Mellitus (NIDDM).

Twenty-one patients on a glyburide regimen of 5 mg QD or 10 mg BID for at least three months completed the study. On Days 1-7, patients were randomized to receive glyburide with either celecoxib 200 mg BID or placebo BID. On Days 12-18, subjects were crossed over to receive glyburide and the alternate treatment of either celecoxib or placebo. Blood glucose and insulin levels and plasma concentrations of celecoxib and glyburide were determined on various days. The detailed study design is given in Appendix 1 (p. 150).

Celecoxib plasma concentrations: The trough celecoxib levels on Days 4-7 and 15-18 showed no significant day effect, indicating steady state levels were reached. The celecoxib AUC and Cmax values for the glyburide 5 mg QD dose group (tabulated below) were comparable to previously observed values. The 10 mg BID dose group had

a 19% higher Cmax and AUC than the 5 mg QD dose group.

Mean celecoxib parameter values (±SD)

Parameter*	Glyburide 5mg QD Group n=10	Glyburide 10 mg BID Group n =14
$AUC_{0\text{-}12\ hr}$ (ng/mL*hr)	8177.7 (3965.1)	9748.1 (6289.2)
$AUC_{0\text{-}24\ hr}$ (ng/mL*hr)	16240.0 (8244.8)	-
C_{max} (ng/mL)	1211.0 (373.3)	1435.9 (767.0)
T_{max} (hr)	6.73 (7.13) 2.53** (0.84)	2.50 (0.76)

*The parameter values were based on profiles of 0-12 hours postdose for the 10 mg BID group and 0-24 hrs for the 5 mg QD group.

**Calculated by excluding 2 subjects who had a very long Tmax.

Effect of celecoxib on glyburide pharmacokinetics: The mean plasma glyburide concentration-time profiles were similar (difference<10%) for the glyburide 10 mg BID group whether glyburide was coadministered with placebo or celecoxib. For the 5 mg QD group, mean plasma concentrations were higher up to 3 hours postdose when glyburide was coadministered with celecoxib, but the opposite was observed between 6-8 hours postdose.

Mean pharmacokinetic parameters (±SD) are tabulated below for the glyburide 5 mg QD and 10 mg BID groups. The differences in the mean Cmax and AUC between the two treatment groups (glyburide + celecoxib vs. glyburide + placebo) for either glyburide dose were within 10% and were not statistically significant as evidenced by the 95% CI values. (Note: The power for detecting a 20% difference was low.)

Mean glyburide parameter values (±SD)

Parameter	Glyburide 5 mg QD (n=7)			Glyburide 10 mg BID (n=14)		
	Placebo BID	Celecoxib 200 mg BID	Ratio* (%) & 95% CI	Placebo BID	Celecoxib 200 mg BID	Ratio* & 95% CI
$AUC_{0\text{-}12\ hr}$ (ng/mL*hr)	1011.24 (444.2)	1023.5 (291.9)	105.3	2117.1 (752.7)	2183.6 (781.3)	103.4
$AUC_{0\text{-}24\ hr}$ (ng/mL*hr)	1227.1 (506.3)	1264.6 (371.8)	105.7	-	-	-
C_{max} (ng/mL)	172.63 (66.0)	157.39 (53.4)	91.3	340.7 (130.2)	363.4 (111.8)	108.4
T_{max} (hr)	5.14 (1.95)	4.58 (1.81)	-	2.43 (1.65)	2.64 (2.80)	-

*(glyburide + celecoxib) / (glyburide + placebo)

By combining all subjects in this study and using the glyburide dose-normalized parameter values, the analysis indicated that there was no statistically significant difference between the two treatments (coadministration with celecoxib and coadministration with placebo) at a power of ≥ 0.80.

Blood glucose concentrations: The treatment group receiving celecoxib had comparable baseline (Day 0) blood glucose concentrations to that receiving placebo. This was true

for both glyburide dose groups. The blood glucose levels as determined on Days 7 and 18 were used to estimate the area under the blood glucose concentration-time curve (AUC), peak glucose concentration (Cmax) and time to peak (Tmax) for the two treatment groups after coadministration. The mean parameter values for both glyburide dose groups are tabulated below. An analysis of variance indicated that the two treatments were not statistically significantly different in both AUC and Cmax (α=0.05). (The power for detecting a 20% difference for both AUC and Cmax was >0.8.)

Mean Blood glucose parameter values (±SD)

Parameter	Glyburide 5 mg QD			Glyburide 10 mg BID		
	Placebo BID	Celecoxib 200 mg BID	Ratio[1] (%) & p-Value	Placebo BID	Celecoxib 200 mg BID	Ratio[1] (%) & p-Value
$AUC_{0\text{-}12\ hr}$ (mg/dL*hr)	1766.9 (±594.7)	1891.3 (±425.9)	100.6 (±0.862)	2740.6 (±737.1)	2849.2 (±985.6)	102.0 (±0.723)
$AUC_{0\text{-}24\ hr}$ (mg/dL*hr)	3512.1 (±1094.8)	3541.4 (±839.2)	95.9 (±0.171)	-	-	-
C_{max} (mg/dL)	242.3 (±59.0)	244.6 (±40.2)	95.3 (±0.165)	325.2 (±49.7)	327.7 (±92.8)	98.7 (±0.786)
T_{max} (hr)	1.01 (±0.015)	1.44 (±0.533)	-	1.86 (±0.86)	2.08 (±1.33)	-
C_{avg} (mg/dL)	144.5 (±44.8)	135.6 (±32.7)	-	-	-	-

[1](glyburide + celecoxib)/(glyburide + placebo)

Plasma insulin concentrations: Plasma insulin concentrations fluctuated appreciably within a 24-hour time period, ranging from approximately 10 to 80 μU/mL. Again, AUC, Cmax and Tmax for the two treatment groups (glyburide+celecoxib and glyburide+placebo) were estimated from the plasma concentration-time profiles. The mean parameter values are tabulated below. Although the differences between the two treatments were not statistically significant (p>0.05), the power for detecting a 20% difference was low (<0.8).

Parameter	Glyburide 5 mg QD			Glyburide 10 mg BID		
	Placebo BID	Celecoxib 200 mg BID	Ratio[1] (%) & p-Value	Placebo BID	Celecoxib 200 mg BID	Ratio[1] (%) & p-Value
$AUC_{0\text{-}12\ hr}$ (µU/mL*hr)	356.6 (195.9)	405.5 (265.3)	104.7 (0.603)	432.7 (311.4)	484.1 (353.6)	107.6 (0.449)
$AUC_{0\text{-}24\ hr}$ (µU/mL*hr)	653.2 (291.2)	732.5 (417.1)	104.1 (0.684)	-	-	-
C_{max} (µU /mL)	79.68 (52.11)	83.01 (65.18)	98.6 (0.849)	67.84 (42.95)	72.69 (50.02)	104.3 (0.720)
T_{max} (hr)	3.51 (5.07)	2.01 (0.58)	-	2.64 (1.74)	2.86 (1.87)	-
C_{avg} (µU/mL)	10.86 (8.78)	12.13 (4.95)	-	-	-	-

[1](glyburide + celecoxib)/(glyburide + placebo)

Conclusion:

Coadministration of celecoxib 200 mg BID with either glyburide 5 mg QD or 10 mg BID in subjects with Type II non-insulin dependent diabetes mellitus did not appear to alter the pharmacokinetic and pharmacodynamic profiles of glyburide.

Reviewer's comments:

1. The patients in this study did not seem to have their blood glucose levels under control. High values were observed during the study. Therefore, the pharmacodynamic results are unreliable for evaluation of drug-drug interactions.

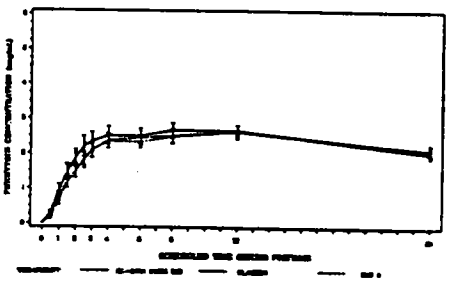
2. Figures 1, 2, 3 in Study Report #N49-97-06-039 was plotted using time as a categorical variable (instead of as a continuous variable).

Phenytoin (Study 050)

Phenytoin, an antiepileptic drug, is metabolized via CYP2C9. Optimum control without clinical signs of toxicity occurs within the narrow range of serum levels between 10 and 20 μg/mL. The primary objective of this study was to determine the single-dose pharmacokinetics of phenytoin in the presence of multiple doses of celecoxib or placebo. The study tested these parameters through the single dose administration of phenytoin to subjects before receiving celecoxib, and again after steady-state blood levels of celecoxib had been achieved. Sixteen healthy subjects completed the study. The detailed study design is given in Appendix 1 (p. 158).

Plasma celecoxib concentrations: The mean plasma celecoxib concentrations reached a maximum of 1105 (±456) ng/mL at 2.3 (±0.95) hours postdose with a mean $AUC_{0\text{-}12\ hr}$ of 6625 (±2490) ng.hr/mL. These values were similar to those reported previously.

Plasma phenytoin and metabolite concentrations: When phenytoin was administered alone (Day 0), mean plasma phenytoin concentrations reached the highest (2.79 μg/mL) at 11.4 hours postdose and decreased to 2.15 μg/mL at 24 hours postdose with an $AUC_{0\text{-}24}$ of 53.9 μg.hr/mL. When phenytoin was coadministered with placebo, the mean plasma phenytoin concentration profile closely followed the Day 0 profile. After coadministration of phenytoin with celecoxib, the mean plasma phenytoin concentrations were generally higher than the Day 0 values. Most of the plasma samples had parahydroxyl metabolite concentrations below the lower limit of quantitation and, therefore, no further evaluation on the metabolite was made.



The mean plasma pharmacokinetic parameter values are tabulated below. The 95% confidence intervals for AUC and Cmax indicated that there were no statistically significant difference between the two treatments (phenytoin + celecoxib vs. phenytoin +

placebo). However, the mean Tmax was shorter for subjects receiving celecoxib (8.6 hrs vs. 11.6 hrs).

Mean Plasma Phenytoin Parameter Values (±SD) (n=16)

Parameter	Phenytoin + placebo	Phenytoin + Celecoxib	Ratio	95% CI
$AUC_{0\text{-}24\ hr}$ (μg/mL*hr)	53.75 ± 15.46	55.55 ± 13.97	104.2	95.3 - 113.9
C_{max} (μg/mL)	2.87 ± 0.82	2.92 ± 0.76	102.1	93.9 - 111.1
T_{max} (hr)	11.6 ± 6.9	8.6 ± 5.5	-	-

Conclusion: Coadministration of celecoxib did not alter the single-dose pharmacokinetic profile of phenytoin as compared to that observed in the presence of placebo.

Comments:

1. Assay method and method validation for plasma parahydroxyl metabolite were not provided.
2. Urine data for both phenytoin and parahydroxyl metabolite were not submitted.

POPULATION PK ANALYSIS IN OA AND RA PATIENTS

The objectives of this population PK analysis were to characterize the celecoxib pharmacokinetics in OA and RA patients and to investigate fourteen covariates on their influences on the apparent volume of distribution (V/F) and plasma clearance (CL/F) of celecoxib. The analysis utilized data from OA or RA patients receiving celecoxib 50, 100, 200 or 400 mg BID in two clinical trials. Each patient had three blood samples drawn (each one hour apart) 7 to 28 days after the first dose with the blood sampling time varying from patient to patient. A total of 326 plasma concentrations were obtained from 110 patients. Tables 1-3 in Appendix 1 (p. 162) present the sample size by study and dose, and descriptive statistics of the covariates for these patients.

Model: A steady-state one compartment model was used to fit the pharmacokinetic data with the NONMEM program. The covariate analysis identified race and body weight as influential factors on CL/F. None of the covariates investigated were found to be influential on V/F. The final model is presented in Appendix 1 (p. 163).

Results: The pharmacokinetic parameter estimates and variabilities are tabulated below.

Parameter	Ka (θ_1), hr^{-1}	V/F (θ_2), L	CL/F , L/hr	Covariates for CL/F		
			Caucasian(θ_3)	Black (θ_4)	Others (θ_5)	Weight (θ_6)
Estimate ± SE	0.372±0.082	141 ± 35	34.7 ± 2.2	0.442±0.070	0.389±0.109	0.831±0.236
%CV*	-	46.6	50.3	-		
σ (%CV)**	33.2			-		

*Intersubject variability **Intrasubject variability

The population mean estimate for V/F was 141 L with an interpatient coefficient of variation (CV) of 47%. For CL/F, the population mean estimate for Caucasians at a median weight of 81.4 kg was 34.7 L/hr. The model estimates a 56% reduction in CL/F

for Blacks and a similar reduction for other non-Caucasians. However, the results for other non-Caucasians are based on data from only three patients. Increases in CL/F were nearly proportional with body weight. The interpatient CV for CL/F was approximately 50%.

Reviewer's comments:
The following comments have been discussed with and concurred by Dr. He Sun, the Pharmacometric node of DPEIII.

1. Regarding the study design:
   a. The 3 blood samples collected within a patient were each taken one hour apart. It is noted that most of the samples were collected 1-5 hours postdose. There were only 27 blood samples collected at or after 8 hours postdose, which were from 10 out of the 110 subjects. Because of the paucity of data at the terminal phase, estimate of CL/F and determination of covariates for CL/F are unreliable. It would have been more advantageous to take three samples from each individual at various absorption/disposition phases. (It is noted that the parameter estimates obtained from this population analysis imply a population mean T1/2 of 2.8 hrs for Caucasians. This is much shorter than the estimates from other studies with dense sampling.) Since this analysis is not of much value, this leaves the sponsor with limited data in OA and RA patients

   b. For each dose taken, we suggest that meal time be recorded in two ways: the time elapse from last meal and from the following meal. This way meal times close to the dosing time will be captured.

2. Regarding the PK model: A one compartment model was used for the analysis but the drug conforms more closely to a two-compartment model.

POPULATION PK/PD ANALYSIS

The sponsor derived a population pharmacokinetic/pharmacodynamic (PK/PD) model to describe the dose-concentration-response relationship for celecoxib analgesia in postsurgical dental patients. In an independent effort, this reviewer also conducted a population PK/PD analysis with Dr. Raymond Miller of Pharmacometrics to characterize the analgesic efficacy of celecoxib in a dental pain trial. The approach employed in both analyses is based on the work of Sheiner[1], Mandema and Stanski[2], and Sheiner et al.[3]. This methodology deals with the complexities associated with analgesia trials: a) repeated measurements, b) ordered categorical responses, and c) nonrandom censoring due to patients taking rescue medication if their pain relief is insufficient.

The sponsor included four dental pain trials in their analysis while this reviewer only had data from one trial (Study 025) at the time of the analysis (IND stage). In the dental pain studies, patients received a single dose of placebo or celecoxib after third molar extraction and blood samples and pain scores were collected at various times up to 24

hours postdose. Remedication was not allowed until 1 hour postdose and no pain scores were taken after patients remedicated. The sample size, dose and the sampling times for each study are given in Appendix 1 (p. 164). NONMEM software was used in both work.

PK Model

There are major differences in the PK models developed by the sponsor and this reviewer. In the analysis, this reviewer also attempted to identify covariates and CL and volume of distribution for the central compartment (V_c) were found to vary with body weight. The models and parameter estimates are shown in Appendix 1 (p. 165).

PD Model

The PD model consisted of modeling the probabilities of remedication and the various degrees of pain relief (PR) based on the methodology first presented by Sheiner et al and later elucidated by Mandema et al. Parameter estimates for the PD model were obtained by maximum likelihood. The pertinent concepts involved in the analysis is described below:

For an individual with a remedication time T and pain relief scores of $Y = (Y_1, Y_2, \ldots, Y_N)$ where Y_t denotes the pain relief score at time t, the likelihood as denoted P(T,Y) is given by the following equation:

$$P(T,Y) = \int P(T,Y \mid \eta)\, P(\eta) d\eta = \int P(T \mid Y,\eta)\, P(Y \mid \eta)\, P(\eta)\, d\eta \qquad (1)$$

where η is a vector of subject specific random effects, assumed to be multivariately normally distributed with mean zero and variance Ω. The likelihood is factored out in two terms, one related to pain relief, $P(Y \mid \eta)$, and one related to the remedication behavior conditional on pain relief, $P(T \mid Y,\eta)$. The model for these two terms are described separately in the following sections.

Model for Pain Relief, $P(Y/\eta)$: Pain relief is an ordered categorical variable with values of 0 (no relief) to 4 (complete relief). For an individual, the probability that Y_t is no less than the score m (m=1, 2, 3 or 4) is related to the placebo effect and drug concentration as shown by the following model:

$$\text{logit}\{P(Y_t \geq m \mid \eta)\} = f_p(m,t) + f_d(C_p) + f_t(t)\eta_Y \qquad (2)$$

where f_p is a function describing the placebo effect, f_d is a function describing the drug effect, f_t is the random effect scaling function, and η_Y is a random individual effect determining the individual sensitivity. The logit transform ensures probabilities between 0 and 1.

Model for Remediation, $P(T|Y,\eta)$ - Survival model: The probability that a patient remains in the study at least to time t is described by the survival function, S(t), which is related to the hazard function, $\lambda(t)$, as shown below:

$$P(T>t \mid Y,\eta) = S(t) = \exp\left(-\int_0^t \lambda(t)dt\right) \qquad (3)$$

The probability of remedication for an individual in the time interval $(t, t+1]$ given they were still in the study in the previous time interval $(t-1, t]$ is given by the equation:

$$P(T=t \mid T \geq t, Y_t = m) = 1 - S(t)/S(t_{-1}) = 1 - \exp\left[-\int_{t-1}^{t} \lambda(t \mid Y_t = m)\, dt\right] \qquad (4)$$

This leads to the following equation that describes the probability of having a remedication time, T, given a set of pain relief score of Y and individual sensitivity of η:

$$P(T \mid Y, \eta) = P(T=t \mid T \geq t, Y_t, \eta) \cdot \prod_{s<t} [1 - P(T=s \mid T \geq s, Y_s, \eta)] \qquad (5)$$

This model implies that the probability of remedication for a patient in a given time interval depends only on the most current PR score and the duration of time in the study. By employing an appropriate hazard function, the observed remedication data are fitted to equation (4) to yield the parameter estimates.

A comparison of the sponsor and this reviewer's PD models and parameter estimates is given in Appendix 1 (p. 166-a). The sponsor indicated that a separate effect compartment was not necessary (i.e., large Keo) and that a simple Emax model was sufficient for modeling the drug effect. These were consistent with our findings during model development.

Sponsor's Revised PK/PD Analysis

After the review of the PK/PD analysis as submitted in the original application, this reviewer made several comments to the sponsor, including the following:

1. Regarding the data set: Patients had two third molar teeth extracted in studies #25 and 27, while only one third molar extracted in studies 70 and 005. Please provide evidence to show that it is reasonable to combine the four studies in the PK/PD analysis. In addition, Study 005 was a single-blind study and it is unclear whether there was bias compared to the other 3 studies.

2. Regarding the PK Model:
   a. A one-compartment model was used in the population PK analysis. This reviewer had plotted several PK profiles on semi-log scale which revealed a biexponential decline. The residual plots from PK modeling as submitted in the NDA also appear to indicate so. Please explain.
   b. V/F was considered to increase with dose while CL/F remained constant over the dose range of interest. This implies the Kel decreased with dose. Please explain in terms of pharmacokinetic characteristics of the drug.

In response to those comments, the sponsor submitted a revised PK/PD analysis (p. 166-b). The changes are noted below:

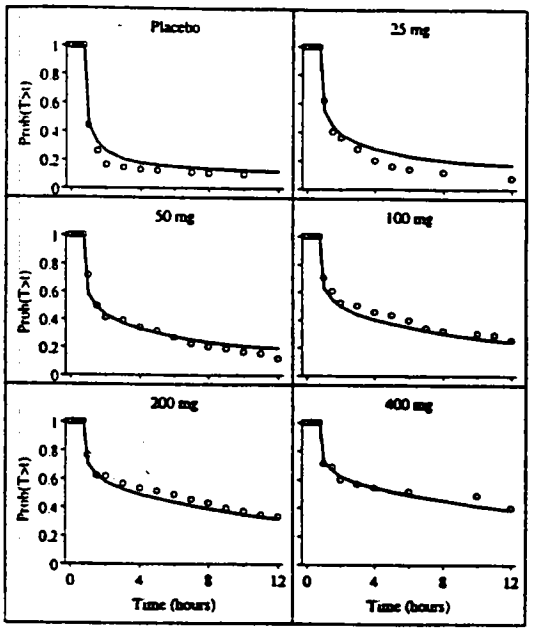
1. Study 005 (single-blind study) is excluded from the PK/PD analysis. (Study 070 is included in the analysis. The sponsor explained that only 1.4% of patients had one molar extracted while the vast majority had two or more molars extracted.)
2. A two-compartment model is used for PK modeling. In addition, Ka and V/F are modeled to vary with dose while micro-constants (k_{12} k_{21} and k_{10}) are kept constant over the dose range. Thus, the sponsor's revised PK model is basically the same as this reviewer's.

Results

The sponsor's data set is superior to this reviewer's in that it had a larger sample size (3-fold) and wider range of doses (25, 50, 100, 200 & 400 mg vs. 25, 50 & 200 mg). The following sections present the sponsor's simulation results based on the pain relief and survival model parameter estimates obtained from the revised PK/PD analysis.

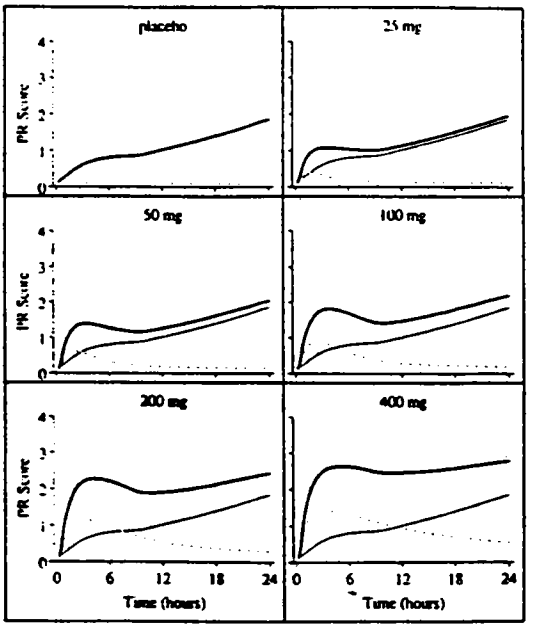
Survival curves: The percentage of patients remaining in the study increases with celecoxib dose as shown in the figure below (left panel). At 2 hours after dosing, less than 20% of patients receiving placebo remained in the study while more than 50% of patients receiving 200 mg celecoxib did.

Figure: %Patients Remaining in Study



° : Obseverd
__ : Predicted

Figure: Drug and Placebo Effects



Drug Effect ..... Placebo Effect (fine line)
Total effect (bold line)

Placebo and drug effects: The relative contribution of the placebo and drug effects on the population mean PR scores are illustrated in the above figure (right panel). At low doses, the drug effect greatly diminished after 10 hours and the pain relief scores were similar to those for the placebo.

Adequate pain relief: Patients with at least a moderate level of pain relief (PR≥2) have a low probability (<0.10) of remedicating. Therefore, a PR score of ≥2 is considered an appropriate measure for adequate pain relief. The contour plot of the dose-time-response surface for the percentage of patients with adequate pain relief is shown below. The response surface suggests that maximal pain relief is achieved in approximately 3 hours and that greater than 50% of the patients achieve adequate pain relief at the 400 mg dose. The model predicts that for every doubling of the dose between 50 mg and 200 mg an additional 9% of patients achieve adequate pain relief at peak (See table below). However, doubling from 200 to 400 mg provides only a 5% increment in the peak percentage of responders with adequate pain relief.

Figure: % Patients with Adequate Pain Relief

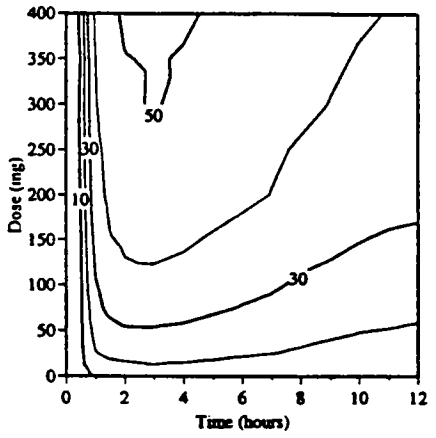


Table: Peak percentages of patients with adequate pain relief.

Dose (mg)	Empirical-Based Estimate (SE)	Model-Based Estimate (90% C.I.)
0	12.3 (7.5)	14.8
25	24.0 (12.3)	25.2
50	35.3 (8.7)	29.3
100	45.7 (7.2)	38.0
200	52.6 (5.5)	46.9
400	51.4 (11.7)	52.1

Conclusion:

Celecoxib single doses in the range of 200-400 mg are predicted to provide adequate pain relief in approximately 50% of the patients. Doses beyond 400 mg are predicted to only provide marginal benefit with less than a 5% increment in the peak percentage of responders with adequate pain relief for every doubling of the dose beyond 400 mg.

References:

1. Sheiner, L.B. A new approach to the analysis of analgesic drug trials, illustrated with bromfenac data. Clin Pharmacol Ther 56(1994): 309-322.
2. Mandema, J.W., and Stanski, D.R. Population pharmacodynamic model for ketorolac analgesia. Clin Pharmacol Ther 60(1996): 619-635.
3. Sheiner, L.B., Beal, S.L., and Dunne, A. Analysis of nonrandomly censored ordered categorical longitudinal data from analgesic trials. JASA 92(1997): 1235-1244.

Reviewer's comment:

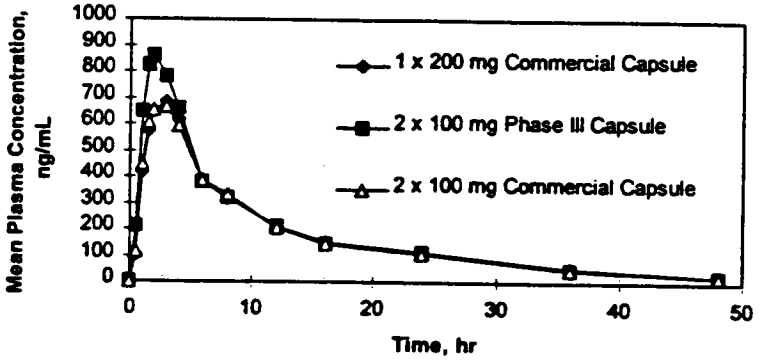
1. In Table IV of the 10/8/98 submission, the empirical-based estimates are provided but it is unclear how these values were obtained.
2. The sponsor did not provide the simulation results regarding the onset time and duration for each dose.
3. The food effect studies suggest that the absorption process for celecoxib may be prolonged due to the poor solubility of the drug making it necessary to have a more complex model to fully describe it. However, the overall PK/PD model appears adequate in describing the PD outcomes for the doses studied.

BIOEQUIVALENCE

a. Commercial Capsules (100 mg & 200 mg) and Phase III 100 mg Capsules (Study 084)

This was a randomized, single dose, three-way crossover study to assess the bioequivalence of the 100 mg and 200 mg commercial capsules to the Phase III 100 mg capsules (given at a dose of 200 mg). Forty-seven healthy subjects completed the study. The detailed study design is given in Appendix 1 (p. 167).

In general, the two commercial capsule formulations gave similar mean plasma concentration-time profiles while the 2 x 100 mg Phase III capsule formulation had higher mean plasma concentrations than the two commercial formulations.



One subject (#0035) had only one detectable plasma concentration after dosing with Phase III capsule during Period 3. This subject had a Cmax of 200 and 800 ng/mL for the 200 mg and 100 mg commercial capsules, respectively. Therefore, the mean pharmacokinetic parameters and %CV are tabulated with and without this subject.

Parameter	1 x 200 mg Commercial Capsule		2 x 100 mg Phase III Capsule		2 x 100 mg Commercial Capsule	
	Mean	%CV	Mean	%CV	Mean	%CV
N = 47						
AUC_{0-48} (ng.hr/mL)	8107.1	44.0	8535.5	43.9	7976.6	47.1
AUC_{∞} (ng.hr/mL)	8828.6	48.0	9229.5*	41.9	8640.5	45.6
Cmax (ng/mL)	801.2	45.8	959.5	49.5	815.2	49.8
Tmax (hr)	2.5 ± 1.0	40.2	2.2 ± 0.9	42.2	2.8 ± 1.5	53.2

T1/2 (hr)	12.2 ± 6.4	52.4	10.9±5.4*	49.8	13.5 ± 8.0	58.9
N = 46 (excluding Subject # 0035)						
AUC_{0-48} (ng.hr/mL)	8241.4	42.2	8720.9	40.8	7926.8	47.7
AUC_{∞} (ng.hr/mL)	8977.4	46.3	9229.5	41.9	8569.2	46.1
Cmax (ng/mL)	813.4	44.5	980.1	46.8	816.3	50.3
Tmax (hr)	2.5 ± 1.0	40.7	2.3 ± 0.9	42.1	2.8 ± 1.5	53.9
T1/2 (hr)	12.3 ± 6.4	52.0	10.9 ± 5.4	49.8	13.4 ± 8.0	59.8

*N=46

Bioequivalence between pairs of formulations were assessed based on the 90% confidence intervals for the ratio of least square means for both AUC and Cmax (see table below).

Reviewer's comments:

1. The number of subjects enrolled in the study is twice as high as the usual study (n=24) due to the high intrasubject variability of the drug.
2. Excluding Subject the 100 mg commercial capsules was not bioequivalent to the 100 mg phase III capsules (given as a 200 mg dose) because the 90% CI for the Cmax was outside of the range.
3. When comparing the Commercial 200 mg and Phase III 100 mg capsules, the latter should serve as the reference formulation but the sponsor did it the other way around. Anyway, the study showed that these two formulations were not bioequivalent
4. The two commercial formulations (100 mg and 200 mg capsules) were bioequivalent.

b. 200 mg Phase III Capsules vs. 200 mg Commercial Capsules (Study 044)

This study was of a randomized, four-period, replicated crossover design in healthy adult volunteers. The primary objectives were to determine the bioequivalency between the phase III and commercial capsule formulations and to investigate the safety and tolerability of the two formulations. A secondary objective was to estimate the intrasubject variability of celecoxib PK parameters for each capsule formulation.

Twenty-four subjects were randomized to receive two single doses of each formulation of celecoxib 200 mg capsules on separate occasions under fasted conditions with a 7-day washout. Plasma samples for celecoxib assay were collected at predetermined intervals for 72 hours after each dose. The detailed study design is given in Appendix 1 (p. 175).

Results from plasma data: The mean plasma concentration-time profiles for the two formulations are shown in the figure that follows. As listed in the table below, mean celecoxib C_{max} for the commercial capsules was 6% higher than that for the phase III capsules, while the difference in mean $AUC_{(0-72)}$ was <1%. The two formulations had comparable Tmax and T1/2. The sponsor claimed that bioequivalence of 200 mg phase III and commercial capsules was demonstrated with respect to celecoxib $AUC_{(0-72)}$ and C_{max} [90% CI = (96.0%, 104.6%) and (96.2%, 117.5%), respectively].

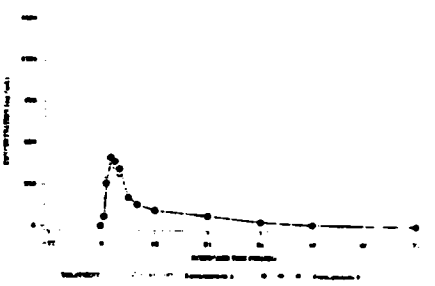


Table: Mean Parameter Values (%CV) and 90% CI for Ratios

Pharmacokinetic Parameter	Commercial Celecoxib 200 mg (N=48)	Phase III Celecoxib 200 mg (N=48)	Ratio[b]: Commercial/ Phase III	90% CI for Ratio
AUC(0-72) (hr·ng/ml)	5166 (24%)	5168 (23%)[c]	100.2%	
C_{max} (ng/ml)	563.8 (41%)	540.4 (43%)[c]	106.3%	
T_{max} (hr)	2.56 (47%)	2.51 (40%)[c]	-	-
Terminal T1/2 (hr)	12.0 (43%)	12.4 (39%)[d]	-	-

[a]arithmetic mean; [b]Ratio based on least square means; [c]N=47; [d]N=46.

The intra- and inter-subject variabilities for AUC_{0-72} and Cmax were computed using SAS PROC VARCOMP. The variabilities were comparable for the two formulations. For AUC, the intra- and inter-subject variabilities were approximately 12% and 20%, respectively. Cmax was more variable (approximately 30% for both intra- and inter-subject variabilities).

Table: Intra- and Inter-subject Variabilities

Parameter[a]	Commercial Capsules (% CV)	Phase III Capsules (% CV)
AUC_{0-72} (ng/mL*hr)		
Intra-subject Variability	11.95	12.26
Between Subjects Variability	20.24	19.24
C_{max} (ng/mL)		

Intra-subject Variability	31.76	29.78
Between Subjects Variability	29.16	32.83

[a] %CV were calculated for log-transformed parameters.

Results from urine data: Only negligible amounts of celecoxib were excreted in urine, which is consistent with other clinical trials. The amount of metabolite M2 (SC-62807) excreted in the urine in the 24 hours after dosing is expressed as a percentage of the celecoxib dose, and is shown in the table below.

Table: Mean Percentage of Dose Excreted in Urine as SC-62807 (0-24 hr)

Day of Dosing	Formulation A (Phase III Capsule)	Formulation B (Commercial Capsule)
1	19.81 ± 5.83	17.95 ± 6.57
8	17.88 ± 4.32	21.04 ± 8.72
15	17.48 ± 5.46	18.81 ± 7.13
22	18.63 ± 7.79	17.83 ± 5.48

Reviewer's comment:
This BE study was of a replicated crossover design but the BE test was based on average bioequivalence. Therefore, the study was forwarded to QMRS of FDA for consult. Bioequivalence of the commercial 200 mg capsules to the Phase III 200 mg capsules was confirmed by Dr. Shan Sun of QMRS

IN VITRO DISSOLUTION

Dissolution test method and test specifications:

Tier 1:

Medium:
Apparatus:
Sampling times:
Specification:

Tier 2:

Medium 1:
Soaking time:
Medium 2:

Apparatus:
Sampling times:

Reviewer's comments:

1. The data as shown in the above table indicates high variability in % dissolved at 30 minutes. Therefore, setting a specification at the time point is considered reasonable. Based on the overall data, the dissolution specification is acceptable.

2. The Tier 2 dissolution method is different from the current USP method

. The Gelatin Capsule Working Group was consulted on this issue before the NDA submission and the method was accepted by the Working Group.